665 to Larm in which heparin is chemically covalently bound to plastic surface materials containing primary amino groups to impart a non-thrombogenic surface to the material. Other approaches for bonding heparin are described in Barbucci, et al., "Coating of commercially available materials with a new heparinizable material", Journal of Biomedical Materials Research, Vol 25, 1259-1274 (1991); Hubbell, J.A., "Pharmacologic Modification of Materials", Cardiovascular Pathology, Vol 2, No 3(Suppl.), 121S-127S (1993); Gravlee, G.P., "Heparin-Coated Cardiopulmonary Bypass Circuits", Journal of Cardiothoracic and Vascular Anesthesia, Vol 8, No 2, pp 213-222 (1994).

With regard to stents, polymeric stents, although effective, may have mechanical properties that are inferior to those of metal stents of like thickness and weave. Metallic vascular stents braided of even relatively fine metal can provide a large amount of strength to resist inwardly directed circumferential pressure. A polymer material of comparable strength requires a much thicker-walled structure or heavier, denser filament weave, which in turn, reduces the cross-sectional area available for flow through the stent and/or reduces the relative amount of open space in the weave. Also, it is usually more difficult to load and deliver polymeric stents using catheter delivery systems.

While certain types of stents such as braided metal stents may be preferred for some applications, the coating and coating modification process of the present invention is not so limited and can be used on a wide variety of prosthetic devices. Thus, in the case of stents, the present invention also applies, for example, to the class of stents that are not self-expanding including those which can be expanded, for instance, with a balloon; and is applicable to polymeric stents of all kinds. Other medical devices that can benefit from the present invention include blood exchanging devices, vascular access ports, central venus catheters, cardiovascular catheters, extracorpeal circuits, vascular grafts, pumps, heart valves, and cardiovascular sutures, to name a few. Regardless of detailed embodiments, applicability of the invention should not be considered limited with respect to implant design, implant location or materials of construction. Further, the present invention may be used with other types of implantable prostheses.

Accordingly, it is a primary object of the present invention to provide a coating and process for coating a stent to be used as a deployed stent prostheses, the coating being capable of effective controlled long-term delivery of biologically active materials.

Another object of the invention is to provide a coating and process for coating a stent prostheses using a biostable hydrophobic elastomer in which biologically active species are incorporated within a coating.

Still another object of the present invention is to provide a multi-layer coating and process for the delivery of biologically active species in which the percentage of active material can vary from layer to layer.

Yet another object of the present invention is to provide a multi-layer coating and process for the delivery of biologically active species from a coating with a non-thrombogenic surface.

A further object of the invention is to provide a multilayer coating for the delivery of biologically active species such as heparin having a fluorosilicone top layer.

A still further object of the invention is to provide a multi-layer coating for the delivery of biologically active species such as heparin having a surface containing immobilized polyethylene glycol (PEG).

Other objects and advantages of the present invention will become apparent to those skilled in the art upon familiarization with the specification and appended claims.

SUMMARY OF THE INVENTION

The present invention provides a relatively thin layered coating of biostable elastomeric material containing an amount of biologically active material dispersed therein in combination with a non-thrombogenic surface that is useful for coating the surfaces of prostheses such as deployable stents.

The preferred stent to be coated is a self-expanding, open-ended tubular stent prostheses. Although other materials, including polymer materials, can be used, in the preferred embodiment, the tubular body is formed of a self-expanding open braid of fine single or polyfilament metal wire which flexes without collapsing, readily axially deforms to an elongate shape for transluminal insertion via a vascular catheter and resiliently expands toward predetermined stable dimensions upon removal in situ.

In the process, the initial coating is preferably applied as a mixture, solution or suspension of polymeric material and finely divided biologically active species dispersed in an organic vehicle or a solution or partial solution of such species in a solvent or vehicle for the polymer and/or biologically active species. For the purpose of this application, the term "finally divided" means any type or size of included material from dissolved molecules through suspensions, colloids and particulate mixtures. The active material is dispersed in a carrier material which may be the polymer, a solvent, or both. The coating is preferably applied as a plurality of relatively thin layers sequentially applied in relatively rapid sequence and is preferably applied with the stent in a radially expanded state.

In many applications the layered coating is referred to or characterized as including an undercoat and topcoat. The coating thickness ratio of the topcoat to undercoat may vary with the desired effect and/or the elution system. Typically these are of different formulations with most or all of the active material being contained in the undercoat and a non-thrombogenic surface is found in the topcoat.

The coating may be applied by dipping or spraying

using evaporative solvent materials of relatively high vapor pressure to produce the desired viscosity and quickly establish coating layer thicknesses. The preferred process is predicated on reciprocally spray coating a rotating radially expanded stent employing an air brush device. The coating process enables the material to adherently conform to and cover the entire surface of the filaments of the open structure of the stent but in a manner such that the open lattice nature of the structure of the braid or other pattern is preserved in the coated device.

The coating is exposed to room temperature ventilation for a predetermined time (possibly one hour or more) for solvent vehicle evaporation. In the case of certain undercoat materials, thereafter the polymer material is cured at room temperature or elevated temperatures. Curing is defined as the process of converting the elastomeric or polymeric material into the finished or useful state by the application of heat and/or chemical agents which induce physico-chemical changes. Where, for example, polyurethane thermoplastic elastomers are used as an undercoat material, solvent evaporation can occur at room temperature rendering the undercoat useful for controlled drug release without further curing.

The applicable ventilation time and temperature for cure are determined by the particular polymer involved and particular drugs used. For example, silicone or polysiloxane materials (such as polydimethylsiloxane) have been used successfully. Urethane pre-polymers can also be utilized. Unlike the polyurethane thermoplastic elastomers, some of these materials are applied as pre-polymers in the coating composition and must thereafter be heat cured. The preferred silicone species have a relatively low cure temperatures and are known as a room temperature vulcanizable (RTV) materials. Some polydimethylsiloxane materials can be cured, for example, by exposure to air at about 90°C for a period of time such as 16 hours. A curing step may be implemented both after application of the undercoat or a certain number of lower layers and the top layers or a single curing step used after coating is completed.

The coated stents may thereafter be subjected to a postcure process which includes an inert gas plasma treatment, and sterilization which may include gamma radiation, ETO treatment, electron beam or steam treatment.

In the plasma treatment, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20-50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. One method uses argon (Ar) gas, operating at a power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to about 100 - 450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

In accordance with the invention, the top coat or surface coating may be applied in any of several ways to further control thrombolitic effects and optionally, control the release profile especially the initial very high release rate associated with the elution of heparin.

In one embodiment, an outer layer of fluorosilicone (FSi) is applied to the undercoat as a topcoat. The outer layer can also contain heparin. In another embodiment, polyethylene glycol (PEG) is immobilized on the surface of the coating. In this process, the underlayer is subjected to inert gas plasma treatment and immediately thereafter is treated by ammonia (NH_3) plasma to aminate the surface. Amination, as used in this application, means creating mostly imino groups and other nitro containing species on the surface. This is followed by immediate immersion into electrophillically activated polyethylene glycol(PEG) solution with a reductive agent, i.e., sodium cyanoborohydride.

The coated and cured stents having the modified outer layer or surface are subjected to a final gamma radiation sterilization nominally at 2.5-3.5 Mrad. Argon (Ar) plasma treated stents enjoy full resiliency after radiation whether exposed in a constrained or non-constrained status, while constrained stents subjected to gamma sterilization without Ar plasma pretreatment lose resiliency and do not recover at a sufficient or appropriate rate.

The elastomeric materials that form the stent coating underlayers should possess certain properties. Preferably the layers should be of suitable hydrophobic biostable elastomeric materials which do not degrade. Surface layer material should minimize tissue rejection and tissue inflammation and permit encapsulation by tissue adjacent the stent implantation site. Exposed material is designed to reduce clotting tendencies in blood contacted and the surface is preferably modified accordingly. Thus, underlayers of the above materials are preferably provided with a fluorosilicone outer coating layer which may or may not contain imbedded bioactive material, such as heparin. Alternatively, the outer coating may consist essentially of polyethylene glycol (PEG), polysaccharides, phospholipids, or combinations of the foregoing.

Polymers generally suitable for the undercoats or underlayers include silicones (e.g., polysiloxanes and substituted polysiloxanes), polyurethanes, thermoplastic elastomers in general, ethylene vinyl acetate copolymers, polyolefin elastomers, polyamide elastomers, and EPDM rubbers. The above-referenced materials are considered hydrophobic with respect to the contemplated environment of the invention. Surface layer materials include fluorosilicones and polyethylene glycol (PEG), polysaccharides, phospholipids, and combinations of the foregoing.

While heparin is preferred as the incorporated active material, agents possibly suitable for incorpora-

tion include antithrombotics,anticoagulants, antibiotics antiplatelet agents, thrombolytics, antiproliferatives, steroidal and non-steroidal antiinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters and drugs that may enhance the formation of healthy neointimal tissue, including endothelial cell regeneration. The positive action may come from inhibiting particular cells (e.g., smooth muscle cells) or tissue formation (e.g., fibromuscular tissue) while encouraging different cell migration (e.g., endothelium) and tissue formation (neointimal tissue).

Suitable materials for fabricating the braided stent include stainless steel, tantalum, titanium alloys including nitinol (a nickel titanium, thermomemoried alloy material), and certain cobalt alloys including cobalt-chromium-nickel alloys such as Elgiloy® and Phynox®. Further details concerning the fabrication and details of other aspects of the stents themselves, may be gleaned from the above referenced U.S. Patents 4 655 771 and 4 954 126 to Wallsten and 5 061 275 to Wallsten et al, which are incorporated by reference herein.

Various combinations of polymer coating materials can be coordinated with biologically active species of interest to produce desired effects when coated on stents to be implanted in accordance with the invention. Loadings of therapeutic materials may vary. The mechanism of incorporation of the biologically active species into the surface coating, and egress mechanism depend both on the nature of the surface coating polymer and the material to be incorporated. The mechanism of release also depends on the mode of incorporation. The material may elute via interparticle paths or be administered via transport or diffusion through the encapsulating material itself.

For the purposes of this specification, "elution" is defined as any process of release that involves extraction or release by direct contact of the material with bodily fluids through the interparticle paths connected with the exterior of the coating. "Transport" or "diffusion" are defined to include a mechanism of release in which the material released traverses through another material.

The desired release rate profile can be tailored by varying the coating thickness, the radial distribution (layer to layer) of bioactive materials, the mixing method, the amount of bioactive material, the combination of different matrix polymer materials at different layers, and the crosslink density of the polymeric material. The crosslink density is related to the amount of crosslinking which takes place and also the relative tightness of the matrix created by the particular crosslinking agent used. This, during the curing process, determines the amount of crosslinking and so the crosslink density of the polymer material. For bioactive materials released from the crosslinked matrix, such as heparin, a denser crosslink structure will result in a longer release time and reduced burst effect.

It will also be appreciated that an unmedicated silicone thin top layer provides some advantage and additional control over drug elusion; however, in the case of heparin, for example, it has been found that a top coat or surface coating modified to further control the initial heparin release profile or to make the surface more non-thrombogenic presents a distinct advantage.

BRIEF DESCRIPTION OF THE DRAWINGS

In the drawings, wherein like numerals designate like parts throughout the same:

FIGURE 1 is a schematic flow diagram illustrating the steps of the process of the invention;

FIGURE 2 represents a release profile for a multilayer system showing the percentage of heparin released over a two-week period;

FIGURE 3 represents a release profile for a multilayer system showing the relative release rate of heparin over a two-week period;

FIGURE 4 illustrates a profile of release kinetics for different drug loadings at similar coating thicknesses illustrating the release of heparin over a two-week period without associated means to provide a long term non-thrombogenic surface thereafter;

FIGURE 5 illustrates drug elution kinetics at a given loading of heparin over a two-week period at different coating thicknesses without associated means to provide a long term non-thrombogenic surface thereafter;

FIGURE 6 illustrates the release kinetics for a given undercoat and topcoat material varied according to thickness in which the percentage heparin in the undercoat and topcoats are kept constant;

FIGURE 7 is a plot of heparin release kinetics in phosphate buffer system at PH 7.4 with and without fluorosilicone (FSi) topcoat; and

FIGURE 8 is another plot of heparin release kinetics in phosphate buffer system in which a topcoat containing fluorosilicone (FSi) only is compared with an FSi topcoat containing 16.7% imbedded heparin.

DETAILED DESCRIPTION

According to the present invention, the stent coatings incorporating biologically active materials for timed delivery in situ in a body lumen of interest are preferably sprayed in many thin layers from prepared coating solutions or suspensions. The steps of the process are illustrated generally in Figure 1. The coating solutions or suspensions are prepared at 10 as will be described later. The desired amount of crosslinking agent (if any) is added to the suspension/solution as at 12 and material is then agitated or stirred to produce a homogenous coating composition at 14 which is thereafter trans-

ferred to an application container or device which may be a container for spray painting at 16. Typical exemplary preparations of coating solutions that were used for heparin and dexamethasone appear next.

General Preparation of Heparin Undercoating Composition

Silicone was obtained as a polymer precursor in solvent (xylene) mixture. For example, a 35% solid silicone weight content in xylene was procured from Applied Silicone, Part #40,000. First, the silicone-xylene mixture was weighed. The solid silicone content was determined according to the vendor's analysis. Precalculated amounts of finely divided heparin (2-6 microns) were added into the silicone, then tetrahydrofuron (THF) HPCL grade (Aldrich or EM) was added. For a 37.5% heparin coating, for example: $W_{silicone}$ = 5 g; solid percent = 35%; W_{hep} = 5 x 0.35x .375/(0.625) = 1.05 g. The amount of THF needed (44 ml) in the coating solution was calculated by using the equation $W_{silicone\ solid}/V_{THF} = 0.04$ for a 37.5% heparin coating solution). Finally, the manufacturer crosslinker solution was added by using Pasteur P-pipet. The amount of crosslinker added was formed to effect the release rate profile. Typically, five drops of crosslinker solution were added for each five grams of silicone-xylene mixture. The solution was stirred by using the stirring rod until the suspension was homogenous and milk-like. The coating solution was then transferred into a paint jar in condition for application by air brush.

General Preparation of Dexamethasone Undercoating Composition

Silicone (35% solution as above) was weighed into a beaker on a Metler balance. The weight of dexamethasone free alcohol or acetate form was calculated by silicone weight multiplied by 0.35 and the desired percentage of dexamethasone (1 to 40%) and the required amount was then weighed. Example: $W_{silicone}$ = 5 g; for a 10% dexamethasone coating, W_{dex} = 5 x 0.35 x 0.1/0.9 = 0.194 g and THF needed in the coating solution calculated. $W_{silicone\ solid}/V_{THF} = 0.06$ for a 10% dexamethasone coating solution. Example: $W_{silicone}$ = 5 g; V_{THF} = 5 x 0.35/0.06 ~ 29 ml. The dexamethasone was weighed in a beaker on an analytical balance and half the total amount of THF was added. The solution was stirred well to ensure full dissolution of the dexamethasone. The stirred DEX-THF solution was then transferred to the silicone container. The beaker was washed with the remaining THF and this was transferred to the silicone container. The crosslinker was added by using a Pasteur pipet. Typically, five drops of crosslinker were used for five grams of silicone.

The application of the coating material to the stent was quite similar for all of the materials and the same for the heparin and dexamethasone suspensions prepared as in the above Examples. The suspension to be applied was transferred to an application device, at 16 in FIGURE 1. Typically a paint jar attached to an air brush, such as a Badger Model 150, supplied with a source of pressurized air through a regulator (Norgren, 0-160 psi) was used. Once the brush hose was attached to the source of compressed air downstream of the regulator, the air was applied. The pressure was adjusted to approximately 15-25 psi and the nozzle condition checked by depressing the trigger.

Any appropriate method can be used to secure the stent for spraying and rotating fixtures were utilized successfully in the laboratory. Both ends of the relaxed stent were fastened to the fixture by two resilient retainers, commonly alligator clips, with the distance between the clips adjusted so that the stent remained in a relaxed, unstretched condition. The rotor was then energized and the spin speed adjusted to the desired coating speed, nominally about 40 rpm.

With the stent rotating in a substantially horizontal plane, the spray nozzle was adjusted so that the distance from the nozzle to the stent was about 2-4 inches and the composition was sprayed substantially horizontally with the brush being directed along the stent from the distal end of the stent to the proximal end and then from the proximal end to the distal end in a sweeping motion at a speed such that one spray cycle occurred in about three stent rotations. Typically a pause of less than one minute, normally about one-half minute, elapsed between layers. Of course, the number of coating layers did and will vary with the particular application. For example, typical tie-layers as at 18 in FIGURE 1, for a coating level of 3-4 mg of heparin per cm^2 of projected area, 20 cycles of coating application are required and about 30 ml of solution will be consumed for a 3.5 mm diameter by 14.5 cm long stent.

The rotation speed of the motor, of course, can be adjusted as can the viscosity of the composition and the flow rate of the spray nozzle as desired to modify the layered structure. Generally, with the above mixes, the best results have been obtained at rotational speeds in the range of 30-50 rpm and with a spray nozzle flow rate in the range of 4-10 ml of coating composition per minute, depending on the stent size. It is contemplated that a more sophisticated, computer-controlled coating apparatus will successfully automate the process demonstrated as feasible in the laboratory.

Several applied layers make up what is called the undercoat as at 18. In one process, additional upper undercoat layers, which may be of the same or different composition with respect to bioactive material, the matrix polymeric materials and crosslinking agent, for example, may be applied as the top layer as at 20. The application of the top layer follows the same coating procedure as the undercoat with the number and thickness of layers being optional. Of course, the thickness of any layer can be adjusted by adjusting the speed of rotation of the stent and the spraying conditions. Generally, the

total coating thickness is controlled by the number of spraying cycles or thin coats which make up the total coat.

As shown at 22 in Figure 1, the coated stent is thereafter subjected to a curing step in which the pre-polymer and crosslinking agents cooperate to produce a cured polymer matrix containing the biologically active species. The curing process involves evaporation of the solvent xylene, THF, etc. and the curing and crosslinking of the polymer. Certain silicone materials can be cured at relatively low temperatures, (i.e. RT-50°C) in what is known as a room temperature vulcanization (RTV) process. More typically, however, the curing process involves higher temperature curing materials and the coated stents are put into an oven at approximately 90°C or higher for approximately 16 hours. The temperature may be raised to as high as 150°C for dexemethasane containing coated stents. Of course, the time and temperature may vary with particular silicones, crosslinkers and biologically active species.

Stents coated and cured in the manner described need to be sterilized prior to packaging for future implantation. For sterilization, gamma radiation is a preferred method particularly for heparin containing coatings; however, it has been found that stents coated and cured according to the process of the invention subjected to gamma sterilization may be too slow to recover their original posture when delivered to a vascular or other lumen site using a catheter unless a pretreatment step as at 24 is first applied to the coated, cured stent.

The pretreatment step involves an argon plasma treatment of the coated, cured stents in the unconstrained configuration. In accordance with this procedure, the stents are placed in a chamber of a plasma surface treatment system such as a Plasma Science 350 (Himont/Plasma Science, Foster City, CA). The system is equipped with a reactor chamber and RF solid-state generator operating at 13.56 mHz and from 0-500 watts power output and being equipped with a microprocessor controlled system and a complete vacuum pump package. The reaction chamber contains an unimpeded work volume of 16.75 inches (42.55 cm) by 13.5 inches (34.3 cm) by 17.5 inches (44.45 cm) in depth.

In the plasma process, unconstrained coated stents are placed in a reactor chamber and the system is purged with nitrogen and a vacuum applied to 20-50 mTorr. Thereafter, inert gas (argon, helium or mixture of them) is admitted to the reaction chamber for the plasma treatment. A highly preferred method of operation consists of using argon gas, operating at a power range from 200 to 400 watts, a flow rate of 150-650 standard ml per minute, which is equivalent to 100 - 450 mTorr, and an exposure time from 30 seconds to about 5 minutes. The stents can be removed immediately after the plasma treatment or remain in the argon atmosphere for an additional period of time, typically five minutes.

After this, as shown at 26, the stents may be exposed to gamma sterilization at 2.5-3.5 Mrad. The radiation may be carried out with the stent in either the radially non-constrained status - or in the radially constrained status.

Preferably, however, the surface is modified prior to plasma treatment or just prior to sterilization by one of several additional processing methods of which some are described in relation to the following examples.

Example 1. Fluorosilicone surface treatment of eluting heparin coating

The undercoat of a stent was coated as multiple applied layers as described above thereafter and cured as described at 22. The heparin content of the undercoat was 37.5% and the coating thickness was about 30-40μ. Fluorosilicone (FSi) spray solution was prepared at 30 from a fluorosilicone suspension (Applied Silicone #40032) by weighing an amount of fluorosilicone suspension and adding tetrahydrofuran (THF) according to the relation equation of V_{THF} = 1.2 x the weight of fluorosilicone suspension. The solution was stirred very well and spray-coated on the stent at 32 using the technique of the application of the undercoat process at 18 and the coated stents were cured at 90°C for 16 hours. The coated stents are argon plasma treated prior to gamma sterilization according to the procedures described above in accordance with steps 22-26.

Figure 7 is a plot of heparin release kinetics in phosphate buffer system with fluorosilicone topcoat and without any topcoat. The thickness of the topcoat is about 10-15μ. While it does not appear on the graph of FIGURE 7, it should be noted that the release rate for the coating without FSi is initially about 25 times higher than that with FSi, i.e., during the first 2 hours. This is, of course, clearly off the scale of the graph. It is noteworthy, however, that the coating with the FSi top layer or diffusion barrier does show a depressed initial release rate combined with an enhanced elusion rate after the first day and through the first week up until about the tenth day. In addition, the fluorosilicone (FSi) topcoat, by virtue of the high electro-negativity of fluorination maintains non-thrombogenic surface qualities during and after the elusion of the biologically active heparin species. In addition, because of the negative charges on the heparin itself, the electro-negativity of the fluorosilicone topcoat may be, at least in part, responsible for the modified heparin release kinetic profile.

FIGURE 8 compares a plot of fluorosilicone (FSi) top coating containing 16.7% imbedded heparin with one containing fluorosilicone (FSi) only. An undercoating is identical to that utilized in FIGURE 7 containing about 37.5% heparin to a thickness of about 30-40 microns. These elution kinetics are quite comparable with the heparin-free FSi top layer greatly reducing the initial burst of heparin release and otherwise the

heparin in the FSi top layer imparts a slightly greater release over the period of the test.

Example 2. Immobilization of polyethylene glycol (PEG) on drug eluting undercoat

An undercoat was coated on a stent and cured at 22 as in Example 1. The stent was then treated by argon gas plasma as at 24 and ammonium gas plasma at 40. The equipment and the process of argon gas plasma treatment was as has been described above. The ammonium plasma treatment was implemented immediately after the argon gas plasma treatment, to aminate the surface of the coating. The ammonium flow rate was in the range of 100-700 cubic centimeter per minute (ccM) in preferably in the range of 500-600 ccM. The power output of radio frequency plasma was in the range of 50-500 watts, preferably in ~200 watts. The process time was in the range of 30sec-10min, preferably -5min.

Immediately after amination, the stents were immersed into electrophilically activated polyethylene glycol (PEG) solution at 42. PEG is known to be an inhibitor of protein absorption. Examples of electrophilically activated PEG are PEG nitrophenyl carbonates, PEG trichlorophenyl carbonates, PEG tresylate, PEG glycidyl ether, PEG isocyanate, etc., optionally with one end terminated with methoxyl group. Molecular weight of PEG ranged from about 1000-6000, and is preferable about 3000. It has been observed that simple ammonium amination will not generate large quantities of primary and secondary amines on the elastomeric polymer surface (for example silicone). Instead, imine (>C=N-H), and other more oxidative nitro containing groups will dominate the surface. It is generally necessary to add reductive agent such as $NaBH_3CN$ into the reaction media so that the functional group on PEG can react with imine and possibly other nitro-containing species on the surface, and therefore immobilize PEG onto the surface. The typical concentration of $NaBH_3CN$ is about 2mg/ml. Since PEG and its derivatives dissolve in water and many polar and aromatic solvents, the solvent used in the coating must be a solvent for PEG but not for the drug in the undercoat to prevent the possible loss of the drug through leaching. In the case of eluting-heparin coating, a mixed solvent of formamide and methyl ethyl ketone (MEK) or a mixed solvent of formamide and acetone are preferred solvents (preferably at ratios of 30 formamide: 70 MEK or acetone by volume), since they will not dissolve heparin. The concentration of PEG, the reaction time, the reaction temperature and the pH value depend on the kind of PEG employed. In the case of eluting heparin coating, 5% PEG tresylate in (30-70) Formamide/MEK was used successfully. The reaction time was 3 hours at room temperature. PEG was then covalently bound to the surface. Gamma radiation was then used for sterilization of this embodiment as previously described.

With respect to the anticoagulant material heparin, the percentage in the undercoat is nominally from about 30-50% and that of the topcoat from about 0-30% active material. The coating thickness ratio of the topcoat to the undercoat varies from about 1:10 to 1:2 and is preferably in the range of from about 1:6 to 1:3.

Suppressing the burst effect also enables a reduction in the drug loading or in other words, allows a reduction in the coating thickness, since the physician will give a bolus injection of antiplatelet/anticoagulation drugs to the patient during the stenting process. As a result, the drug imbedded in the stent can be fully used without waste. Tailoring the first day release, but maximizing second day and third day release at the thinnest possible coating configuration will reduce the acute or subcute thrombosis.

Figure 4 depicts the general effect of drug loading for coatings of similar thickness. The initial elution rate increases with the drug loading as shown in Figure 5. The release rate also increases with the thickness of the coating at the same loading but tends to be inversely proportional to the thickness of the topcoat as shown by the same drug loading and similar undercoat thickness in Figure 6.

What is apparent from the data gathered to date, however, is that the process of the present invention enables the drug elution kinetics to be controlled in a manner desired to meet the needs of the particular stent application. In a similar manner, stent coatings can be prepared using a combination of two or more drugs and the drug release sequence and rate controlled. For example, antiproliferation drugs may be combined in the undercoat and antiplatelet drugs in the topcoat. In this manner, the antiplatelet drugs, for example, heparin, will elute first followed by antiproliferation drugs to better enable safe encapsulation of the implanted stent.

The heparin concentration measurement were made utilizing a standard curve prepared by complexing azure A dye with dilute solutions of heparin. Sixteen standards were used to compile the standard curve in a well-known manner.

For the elution test, the stents were immersed in a phosphate buffer solution at pH 7.4 in an incubator at approximately 37°C. Periodic samplings of the solution were processed to determine the amount of heparin eluted. After each sampling, each stent was placed in heparin-free buffer solution.

As stated above, while the allowable loading of the elastomeric material with heparin may vary, in the case of silicone materials heparin may exceed 60% of the total weight of the layer. However, the loading generally most advantageously used is in the range from about 10% to 45% of the total weight of the layer. In the case of dexamethasone, the loading may be as high as 50% or more of the total weight of the layer but is preferably in the range of about 0.4% to 45%.

It will be appreciated that the mechanism of incorporation of the biologically active species into a thin sur-

face coating structure applicable to a metal stent is an important aspect of the present invention. The need for relatively thick-walled polymer elution stents or any membrane overlayers associated with many prior drug elution devices is obviated, as is the need for utilizing biodegradable or reabsorbable vehicles for carrying the biologically active species. The technique clearly enables long-term delivery and minimizes interference with the independent mechanical or therapeutic benefits of the stent itself.

Coating materials are designed with a particular coating technique, coating/drug combination and drug infusion mechanism in mind. Consideration of the particular form and mechanism of release of the biologically active species in the coating allow the technique to produce superior results. In this manner, delivery of the biologically active species from the coating structure can be tailored to accommodate a variety of applications.

Whereas the above examples depict coatings having two different drug loadings or percentages of biologically active material to be released, this is by no means limiting with respect to the invention and it is contemplated that any number of layers and combinations of loadings can be employed to achieve a desired release profile. For example, gradual grading and change in the loading of the layers can be utilized in which, for example, higher loadings are used in the inner layers. Also layers can be used which have no drug loadings at all. For example, a pulsatile heparin release system may be achieved by a coating in which alternate layers containing heparin are sandwiched between unloaded layers of silicone or other materials for a portion of the coating. In other words, the invention allows untold numbers of combinations which result in a great deal of flexibility with respect to controlling the release of biologically active materials with regard to an implanted stent. Each applied layer is typically from approximately 0.5 microns to 15 microns in thickness. The total number of sprayed layers, of course, can vary widely, from less than 10 to more than 50 layers; commonly, 20 to 40 layers are included. The total thickness of the coating can also vary widely, but can generally be from about 10 to 200 microns.

Whereas the polymer of the coating may be any compatible biostable elastomeric material capable of being adhered to the stent material as a thin layer, hydrophobic materials are preferred because it has been found that the release of the biologically active species can generally be more predictably controlled with such materials. Preferred materials include silicone rubber elastomers and biostable polyurethanes specifically.

This invention has been described herein in considerable detail in order to comply with the Patent Statutes and to provide those skilled in the art with the information needed to apply the novel principles and to construct and use embodiments of the example as required. However, it is to be understood that the invention can be carried out by specifically different devices and that various modifications can be accomplished without departing from the scope of the invention itself.

Claims

1. An implantable medical device having an outer surface covered at least in part by a conformal coating of a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom and means associated with the conformal coating to provide a non-thrombogenic surface after said timed delivery of the biologically active material.

2. The device of claim 1 wherein the conformal coating comprises an amount of finely divided biologically active material in the hydrophobic elastomeric material.

3. The device of claim 2 wherein the finely divided biologically active material has an average particle size of less than about 15 microns.

4. The device of claim 2 wherein the finely divided biologically active material has an average particle site of less than about 10 microns at drug loading of about 25-60 weight percent of the conformal coating.

5. The device of claim 1 wherein the conformal coating comprises an amount of biologically active material molecularly distributed in the elastomeric material.

6. The device of claim 1 wherein the biologically active material is selected from the group consisting of antithrombotics, anticoagulants, antiplatelet agents, thrombolytics, antiproliferatives, steroidal and non-steroidal antiinflammatories, agents that inhibit hyperplasia and in particular restenosis, smooth muscle cell inhibitors, growth factors, growth factor inhibitors, cell adhesion inhibitors, cell adhesion promoters, drugs that enhance the formation of healthy neointimal tissue and combinations thereof.

7. The device of claim 1 wherein the hydrophic elastomeric material is selected from the group consisting of silicones, polyurethanes, ethylene vinyl acetate copolymers, polyolefin elastomers, polyamide elastomers and EPDM rubbers and combinations thereof.

8. The device of claim 1 wherein the conformal coating comprises multiple layers of elastomeric material incorporating an amount of biologically active

material therein.

9. The device of claim 1 wherein the means associated with the conformal coating comprises an outer layer at least partially covering the conformal coating, the outer layer comprising a non-thrombogenic polymeric material.

10. The device of claim 9 wherein the non-thrombogenic polymeric material is selected from the group consisting of fluorosilicone, polyethylene glycol, polysaccharides and phospholipids and combinations thereof.

11. The device of claim 10 wherein the non-thrombogenic polymeric material comprises a fluorosilicone coating adhered to the conformal coating.

12. The device of claim 10 wherein the non-thrombogenic polymeric material comprises a polyethylene glycol covalently bound to an aminated conformal coating.

13. The device of claim 1 where the implanted medical device is formed of metal.

14. An expandable stent for implantation in a body comprising a tubular metal body having open ends and an open lattice sidewall structure and a continuous conformal coating on the surface of said sidewall structure, said coating comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom, wherein said coating conforms to said sidewall structure in a manner that preserves said open lattice and wherein said coating has an outer surface having non-thrombogenic qualities.

15. The device of claim 14 wherein said biologically active material is heparin.

16. The device of claim 15 wherein the outer surface layer of said coating includes a material selected from fluorosilicone, and polyethylene glycol (PEG).

17. The device of claim 16 wherein said outer coating is fluorosilicone.

18. The device of claim 17 wherein said outer layer optionally further comprises an amount of finely divided heparin.

19. The device of claim 16 wherein said outer layer comprises polyethylene glycol (PEG).

20. A stent for implantation in a vascular lumen comprising a tubular body having open ends and a sidewall and a continuous conformal coating on the surface of said sidewall, said coating further comprising an undercoat of a hydrophobic elastomeric material incorporating an amount of finely divided heparin therein for timed delivery therefrom, wherein said coating further comprises a topcoat containing an amount of fluorosilicone.

21. The device of claim 20 wherein said topcoat optionally further comprises an amount of finely divided heparin.

22. A stent for implantation in a vascular lumen comprising a tubular body having open ends and a sidewall and a continuous conformal coating on the surface of said sidewall, said coating further comprising an undercoat of a hydrophobic elastomeric material incorporating an amount of finely divided heparin therein for timed delivery therefrom, wherein said coating further comprises a topcoat containing an amount of polyethylene glycol (PEG).

23. A method of coating an implantable stent protheses with a layer comprising a hydrophobic elastomeric material incorporating an amount of biologically active material therein for timed delivery therefrom comprising the steps of:

(a) applying a topcoat of a formulation containing uncured polymeric material in solvent mixture and an amount of finely divided biologically active species; and
(b) curing said polymeric material;
(c) applying a topcoat of a formulation having qualities which both create a non-thrombogenic surface and modified delivery of said biologically active material.

24. The method of claim 23 wherein the elastomeric material is a silicone and the biologically active material is heparin.

25. The method of claim 24 wherein said topcoat comprises fluorosilicone.

26. The method of claim 25 wherein said topcoat comprises an amount of heparin.

27. The method of claim 24 wherein said topcoat comprises polyethylene glycol (PEG).

28. The method of claim 27 further comprising the steps of:

(d) treating said topcoat after cure with inert gas plasma followed by treatment with ammonia plasma;
(e) applying an outer coating of polyethylene

glycol (PEG) from a solution thereof.

29. The method of claim 28 wherein the polyethylene glycol (PEG) in said solution is selected from PEG nitrophenyl carbonates, PEG trichlorophenyl carbonates, PEG tresylate, PEG glycidylether, PEG isocyanate and combinations thereof.

30. The method of claim 28 wherein the PEG is electrophilically active.

31. The method of claim 28 wherein the PEG has an end terminated with a methoxyl group.

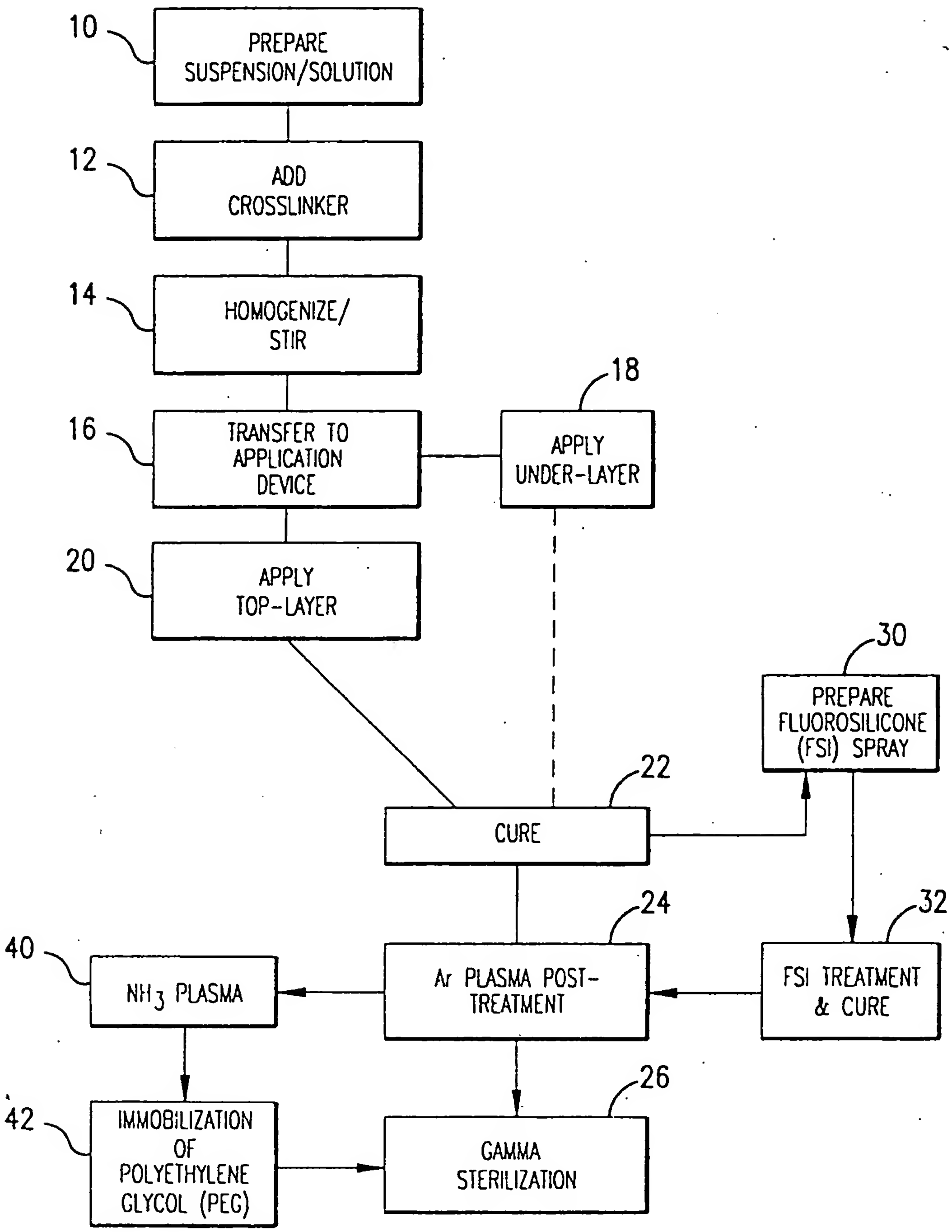

10
PREPARE SUSPENSION/SOLUTION
12
ADD CROSSLINKER
14
HOMOGENIZE/ STIR
16
TRANSFER TO APPLICATION DEVICE
18
APPLY UNDER-LAYER
20
APPLY TOP-LAYER
30
PREPARE FLUOROSILICONE (FSI) SPRAY
22
CURE
24
Ar PLASMA POST-TREATMENT
32
FSI TREATMENT & CURE
40
NH3 PLASMA
42
IMMOBILIZATION OF POLYETHYLENE GLYCOL (PEG)
26
GAMMA STERILIZATION

FIG.1

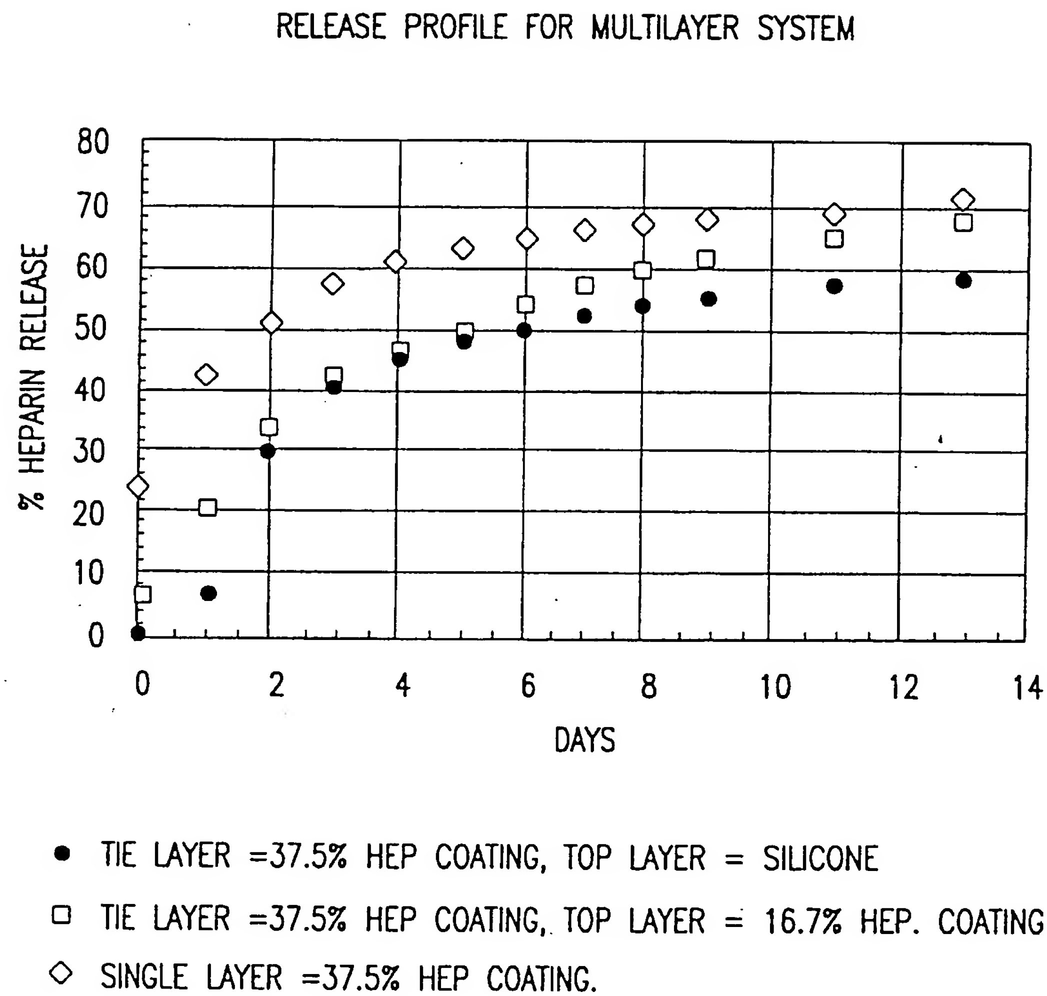

RELEASE PROFILE FOR MULTILAYER SYSTEM
% HEPARIN RELEASE
80
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
DAYS
● TIE LAYER =37.5% HEP COATING, TOP LAYER = SILICONE
□ TIE LAYER =37.5% HEP COATING, TOP LAYER = 16.7% HEP. COATING
◇ SINGLE LAYER =37.5% HEP COATING.

FIG.2

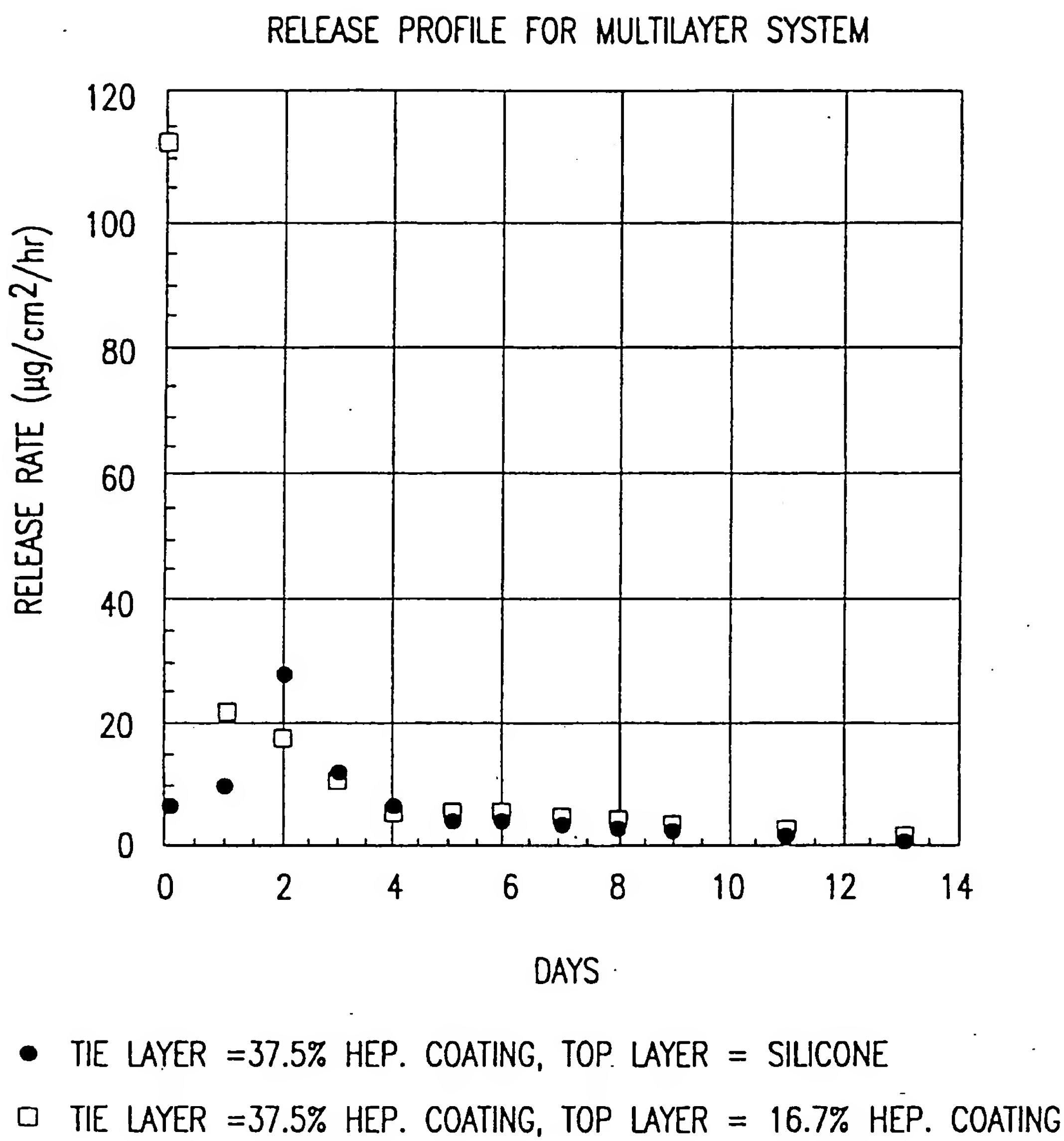

RELEASE PROFILE FOR MULTILAYER SYSTEM
RELEASE RATE (μg/cm2/hr)
120
100
80
60
40
20
0
0
2
4
6
8
10
12
14
DAYS
● TIE LAYER =37.5% HEP. COATING, TOP LAYER = SILICONE
□ TIE LAYER =37.5% HEP. COATING, TOP LAYER = 16.7% HEP. COATING

FIG.3

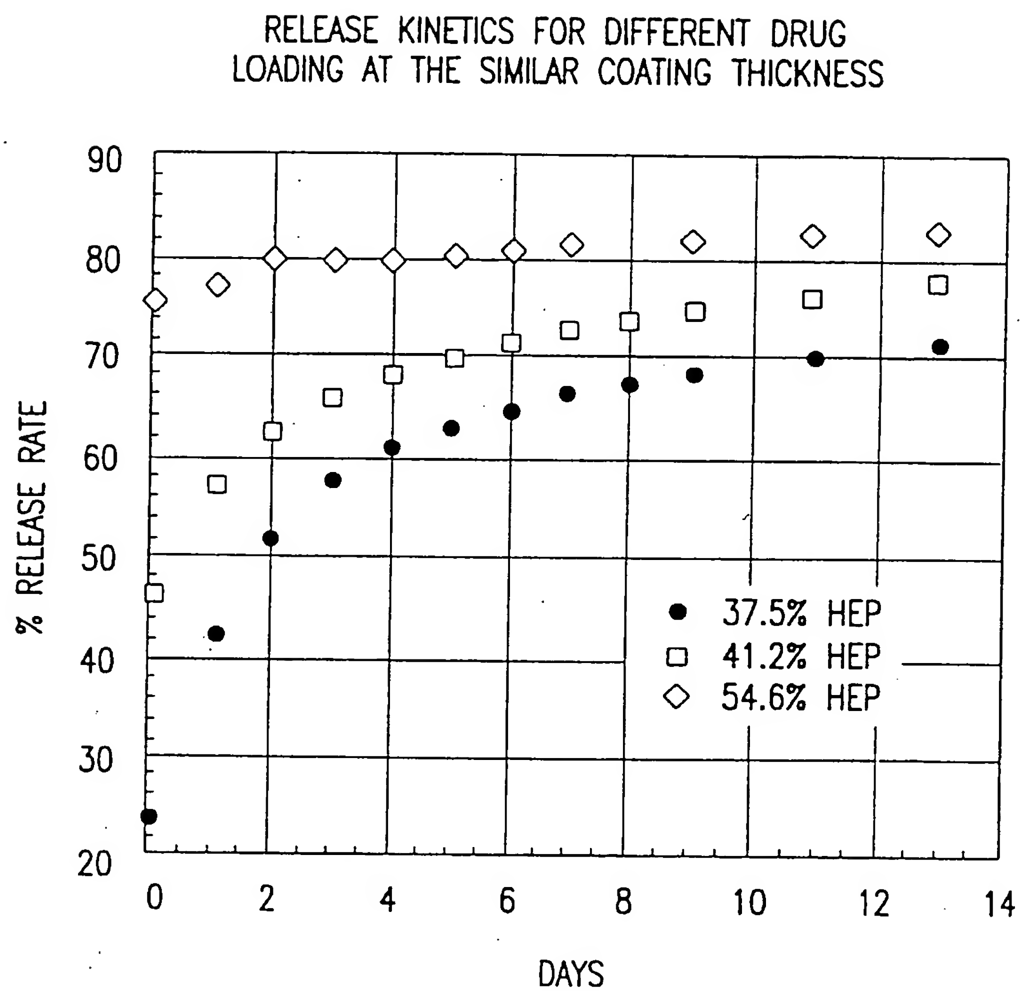

RELEASE KINETICS FOR DIFFERENT DRUG LOADING AT THE SIMILAR COATING THICKNESS
% RELEASE RATE
90
80
70
60
50
40
30
20
0
2
4
6
8
10
12
14
DAYS
37.5% HEP
41.2% HEP
54.6% HEP

FIG.4

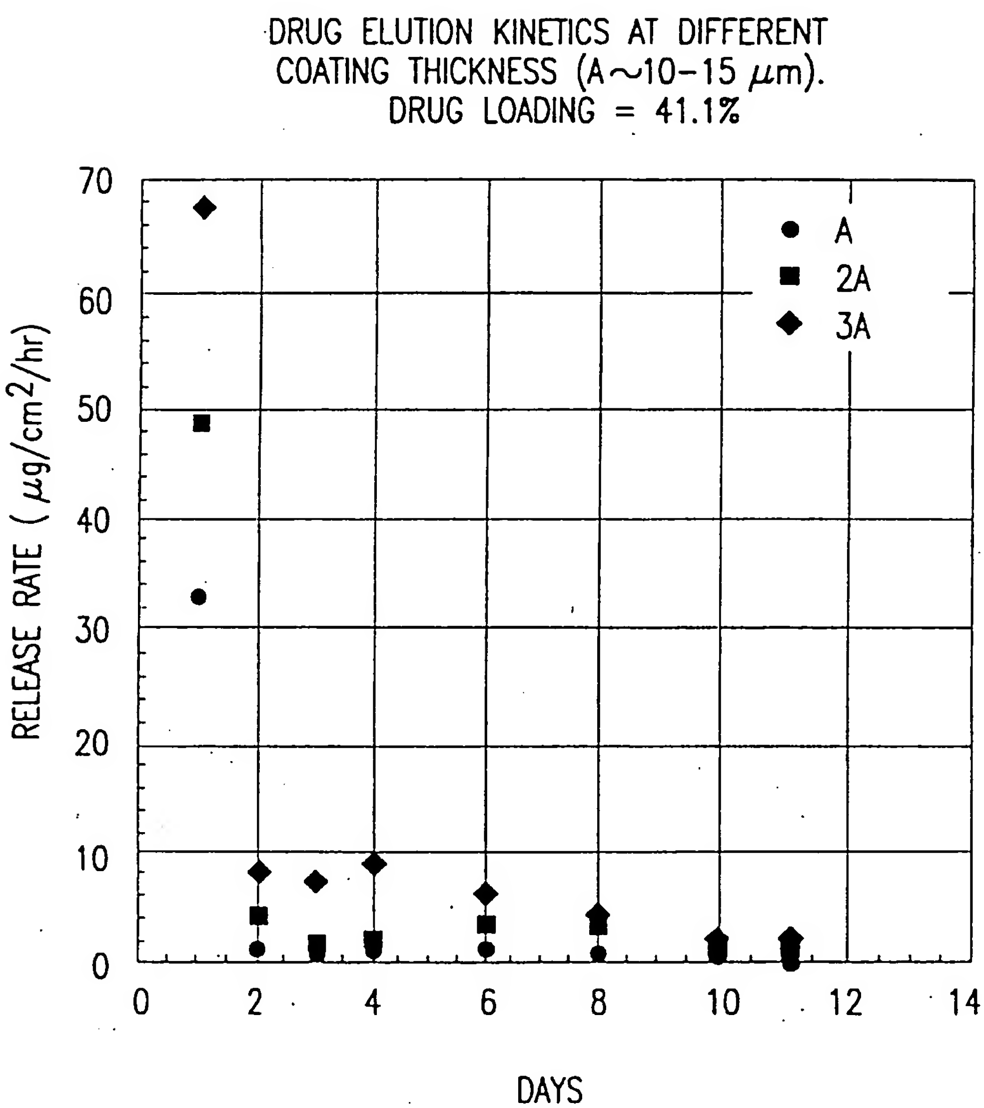

DRUG ELUTION KINETICS AT DIFFERENT
COATING THICKNESS (A~10-15 μm).
DRUG LOADING = 41.1%
RELEASE RATE (μg/cm2/hr)
70
60
50
40
30
20
10
0
0
2
4
6
8
10
12
14
DAYS
A
2A
3A

FIG.5

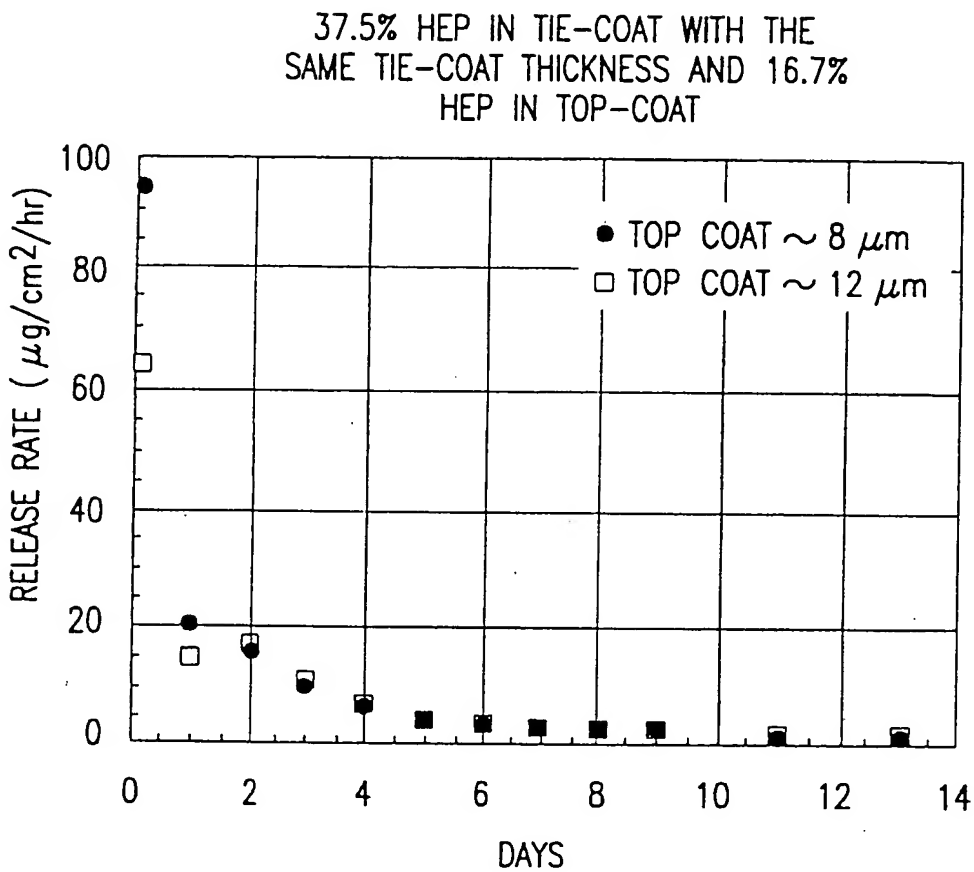

37.5% HEP IN TIE-COAT WITH THE
SAME TIE-COAT THICKNESS AND 16.7%
HEP IN TOP-COAT
RELEASE RATE (μg/cm2/hr)
100
80
60
40
20
0
TOP COAT ~ 8 μm
TOP COAT ~ 12 μm
0
2
4
6
8
10
12
14
DAYS

FIG.6

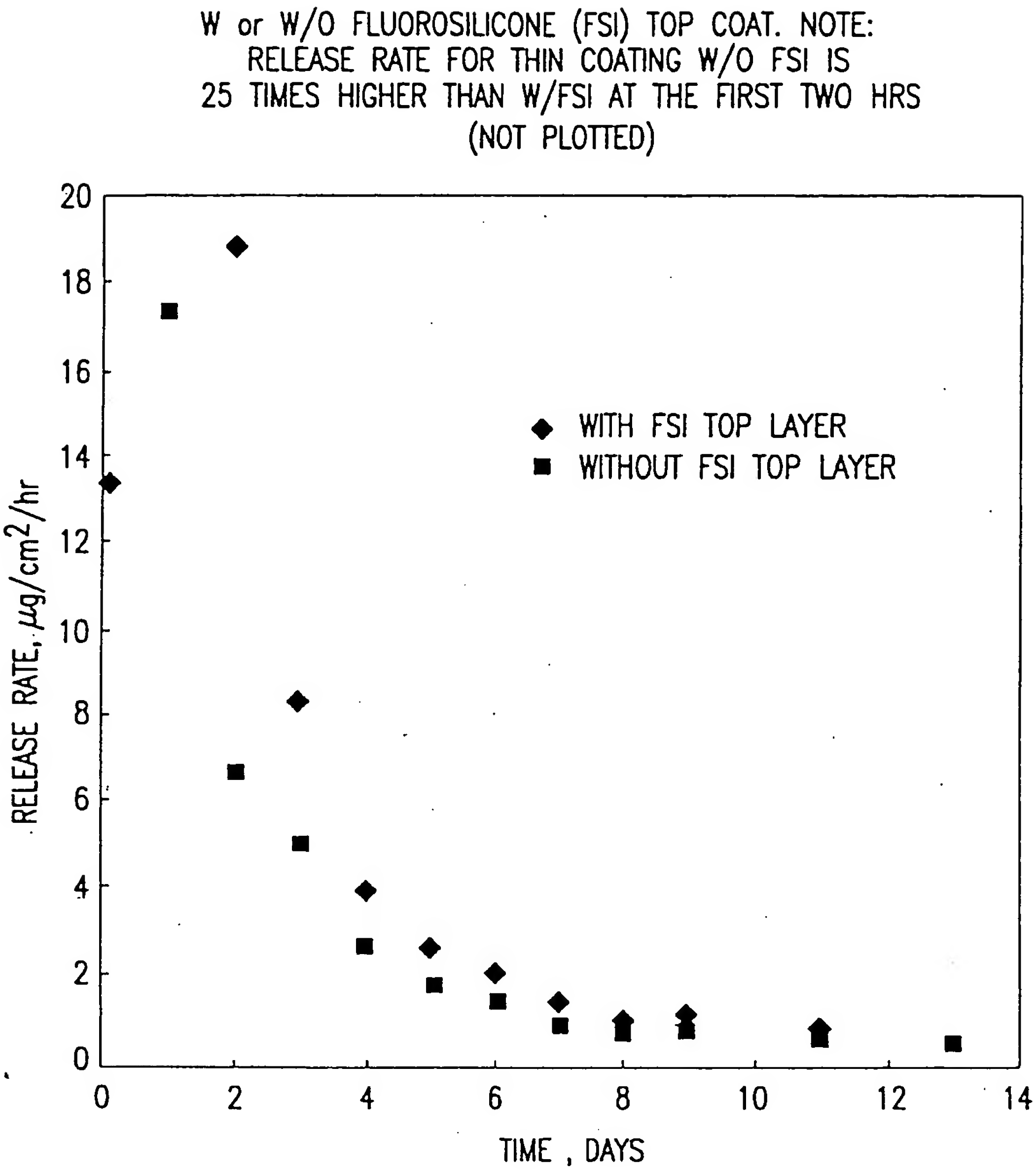
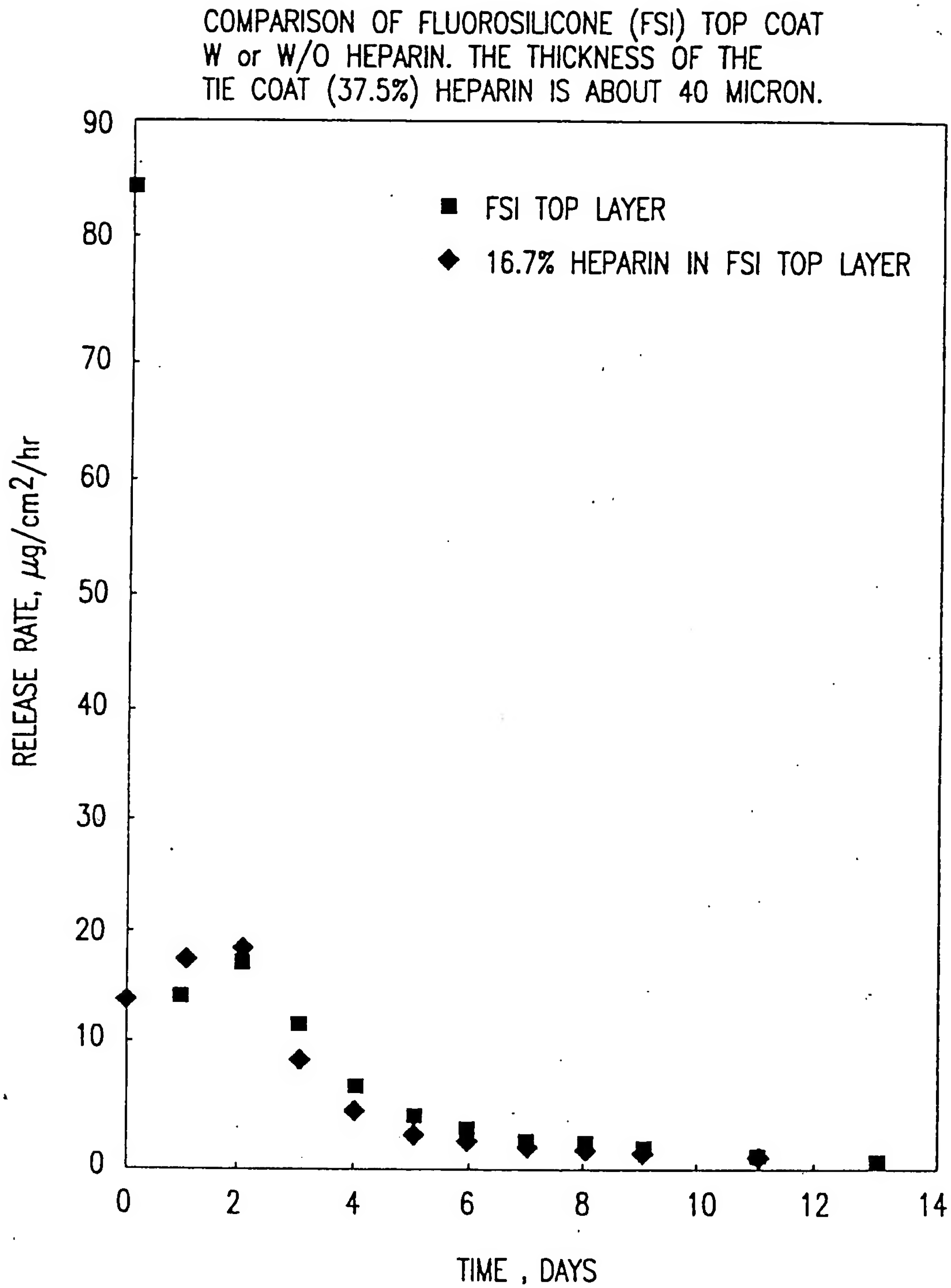

W or W/O FLUOROSILICONE (FSI) TOP COAT. NOTE:
RELEASE RATE FOR THIN COATING W/O FSI IS
25 TIMES HIGHER THAN W/FSI AT THE FIRST TWO HRS
(NOT PLOTTED)
RELEASE RATE, μg/cm2/hr
TIME , DAYS
WITH FSI TOP LAYER
WITHOUT FSI TOP LAYER
0
2
4
6
8
10
12
14
16
18
20

FIG.7



COMPARISON OF FLUOROSILICONE (FSI) TOP COAT
W or W/O HEPARIN. THE THICKNESS OF THE
TIE COAT (37.5%) HEPARIN IS ABOUT 40 MICRON.
FSI TOP LAYER
16.7% HEPARIN IN FSI TOP LAYER
RELEASE RATE, μg/cm2/hr
TIME , DAYS
0
10
20
30
40
50
60
70
80
90
2
4
6
8
10
12
14

FIG.8

(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) EP 0 832 655 A3

(12) EUROPEAN PATENT APPLICATION

(88) Date of publication A3:
16.12.1998 Bulletin 1998/51

(43) Date of publication A2:
01.04.1998 Bulletin 1998/14

(21) Application number: 97109380.2

(22) Date of filing: 10.06.1997

(51) Int. Cl.[6]: **A61L 33/00**, A61F 2/06, A61L 27/00

(84) Designated Contracting States:
AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
Designated Extension States:
AL LT LV RO SI

(30) Priority: 13.06.1996 US 663518

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(54) **Drug release stent coating and process**

(57) A coating and method for implantable open lattice metallic stent prostheses are disclosed. The coating includes a relatively thin layer of biostable elastomeric material containing an amount of biologically active material particularly heparin, dispersed in the coating in combination with a non-thrombogenic surface. In one embodiment, the surface is provided with sites of high electronegativity species by coating with fluorosilicone which aid in controlling elution, particularly the initial release rate, and reduced thrombogenic activity. Other non-thrombogenic outer layers for heparin such as covalently bound polyethylene glycol (PEG) are also disclosed.

EP 0 832 655 A3

European Patent Office

EUROPEAN SEARCH REPORT

Application Number
EP 97 10 9380

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int.Cl.6)
P,X	EP 0 734 721 A (ADVANCED CARDIOVASCULAR SYSTEMS INC.) 2 October 1996 * page 3, column 3, line 44 - column 4, line 7 * * page 3, column 4, line 23 - page 4, column 5, line 32 * * page 4, column 6, line 17 - line 44; claims *	1-10, 13-16, 19, 22-24,27	A61L33/00 A61F2/06 A61L27/00
P,A	EP 0 716 836 A (ADVANCED CARDIOVASCULAR SYSTEMS INC) 19 June 1996 * page 4, column 6, line 58 - page 5, column 7, line 45 * * page 7, column 11, line 18 - line 35; claims *	1,6,7,9, 10, 13-16, 19,22	
A	WO 92 15286 A (NOVA PHARMACEUTICAL CORP) 17 September 1992 * page 7, line 4 - line 10 * * page 10, line 3 - page 11, line 13; claims *	1,6-8, 13-15,23	TECHNICAL FIELDS SEARCHED (Int.Cl.6) A61L
D,A	EP 0 623 354 A (MEDTRONIC INC) 9 November 1994 * claims *	1,6-8, 13-15,23	
A	EP 0 604 022 A (ADVANCED CARDIOVASCULAR SYSTEMS INC) 29 June 1994		

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	26 October 1998	Fletcher, A

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
Y : particularly relevant if combined with another document of the same category
A : technological background
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T : theory or principle underlying the invention
E : earlier patent document, but published on, or after the filing date
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